A Natural Products Primer

Objectives:

What are “natural products”

Where do they come from (source organisms)

What makes them unique among other molecules

Natural products as antibiotics

Natural products:

- Small organic molecules known as secondary metabolites
- Distinct from primary metabolites involved in essential cellular functions (e.g. amino/nuclei acids, sugars, lipids)
- Functions are central to the ecology, biology, existence of producing organism
- Molecules to which enormous energy is expended and as much as 15% of a genome is devoted

"Natural Products"

Primary molecules of living systems include amino acids, nucleic acids, sugars and lipids

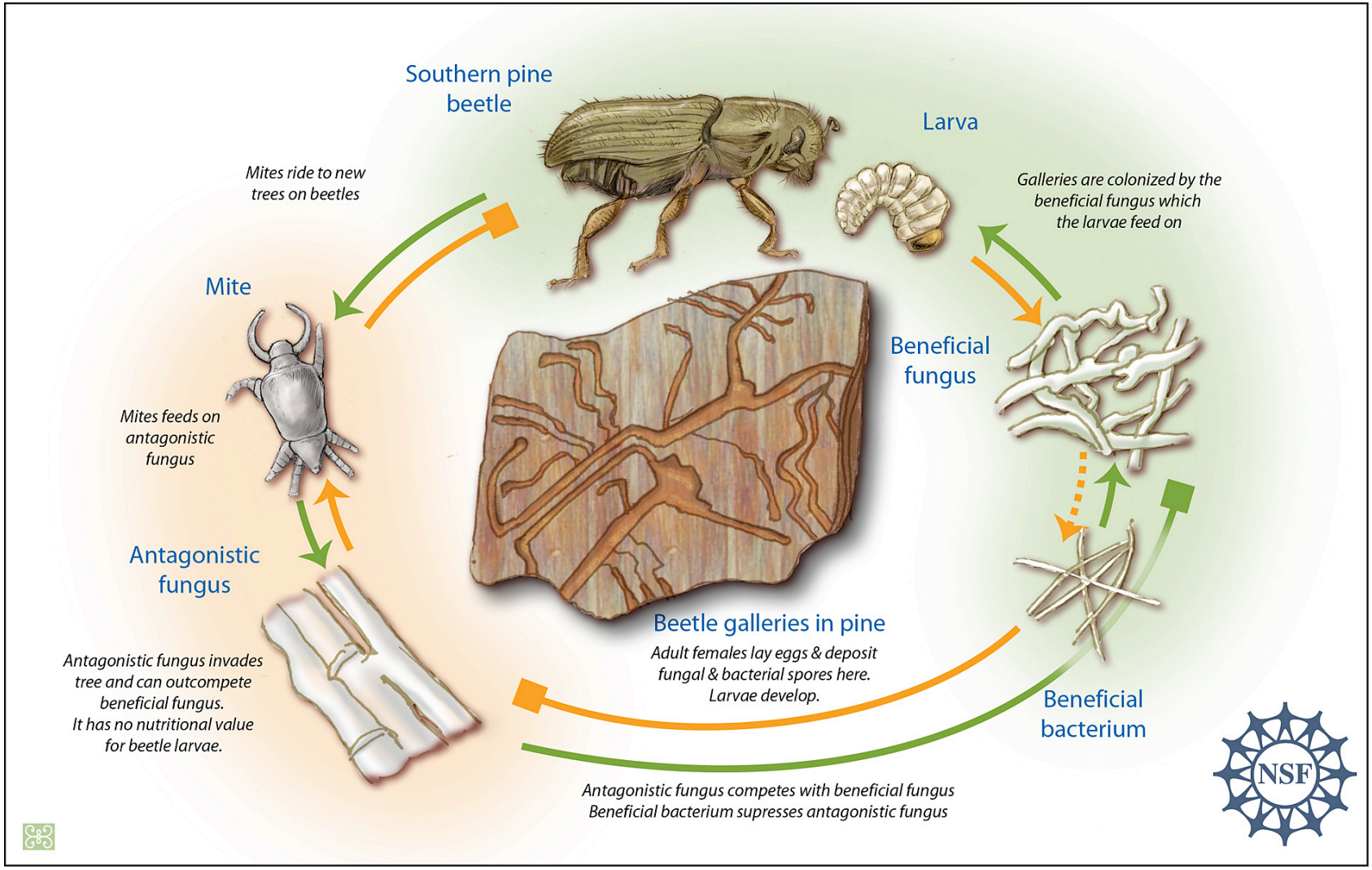
DNA → RNA → proteins → small molecules (NPs)

- "DNA-encoded small molecules"
- Critical in information flow within and between organisms
- In large part controlling ecology: symbioses, complex biological systems

Mutualistic symbiosis among a beetle, a fungus and an actinomycete

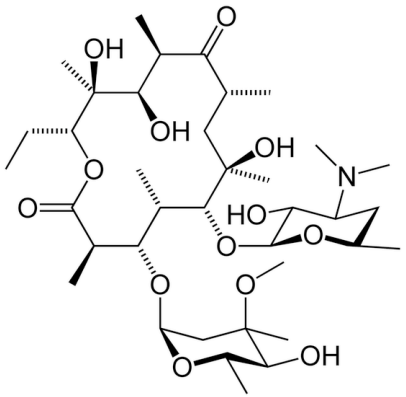
Currie, Clardy, *et al., Science*, 2008,

Daly Lecture, April 28th, 2010, Lipsett Auditorium: Prof. Jon Clardy

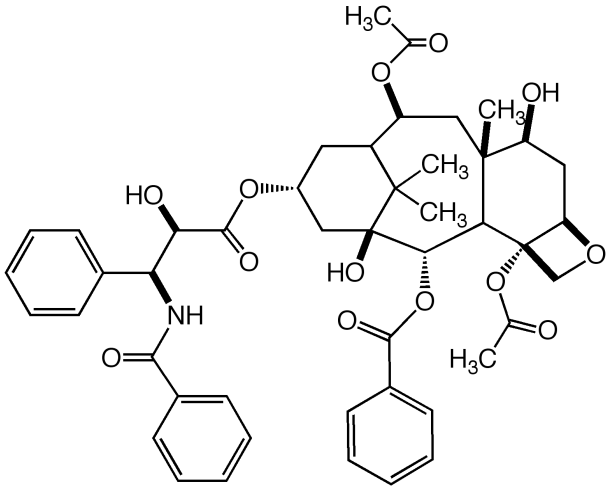


Zina Deretsky, NSF http://www.nsf.gov/news/mmg/media/images/pine_beetle1_h.jpg

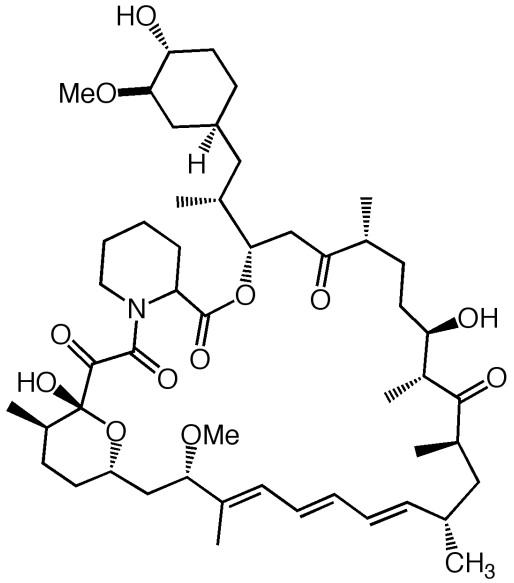
Natural Products ⟺ Complexity



erythromycin
(*S. erythaea*)



Paclitaxel
(TAXOL™)
(*T. brevifolia*)



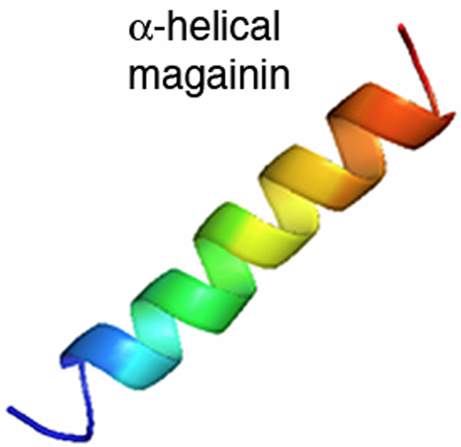
rapamycin
(Rapamune™)
(*Strep. hygroscopicus*)

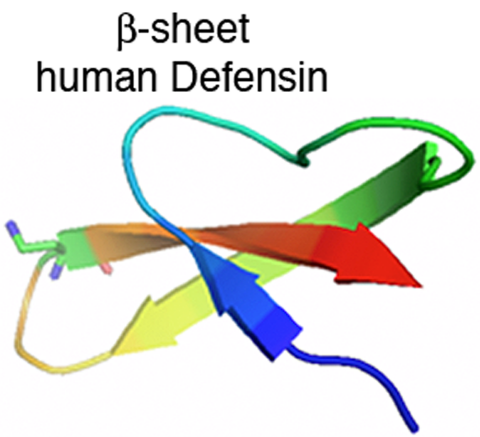
Multiple chiral centers – Complex branching – 3-Dimensionality

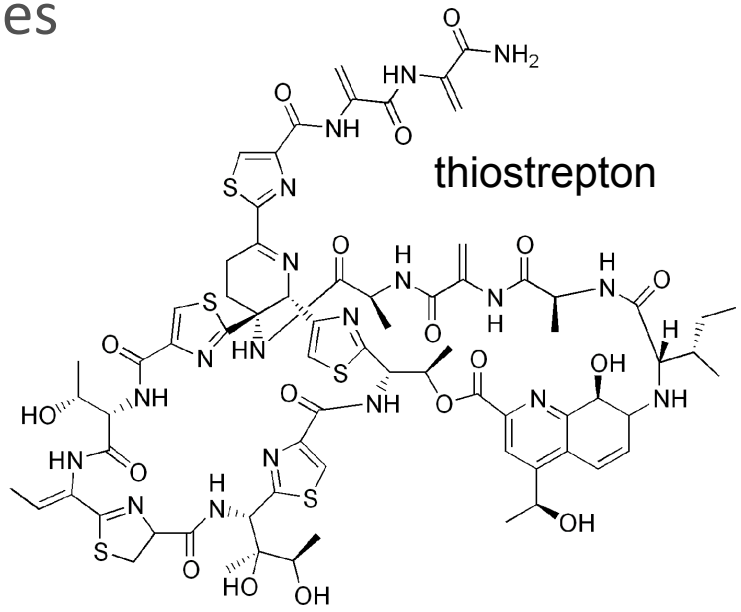
Impact synthetic organic chemistry, enzymology, biosynthesis, bacterial genetics and genomics

Classes of natural products

- Polyketides: erythromycin, rapamycin
- Non-ribosomal peptide synthases (NRPSs): cyclosporins, microcystins
- Hybrid PKS/NRPS: bleomycin, epothilone
- Ribosomally-encoded peptides: cyanobactins, thiostrepton, antimicrobial peptides
- Alkaloids: morphine, epibatadine



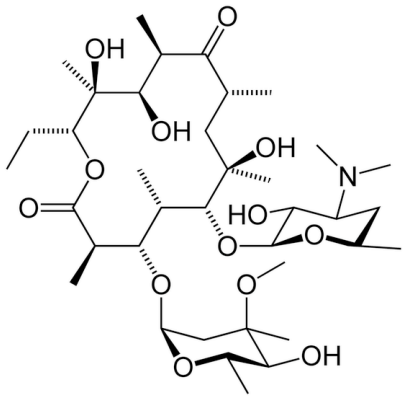




Kelly *et al*., *JACS*, 2009

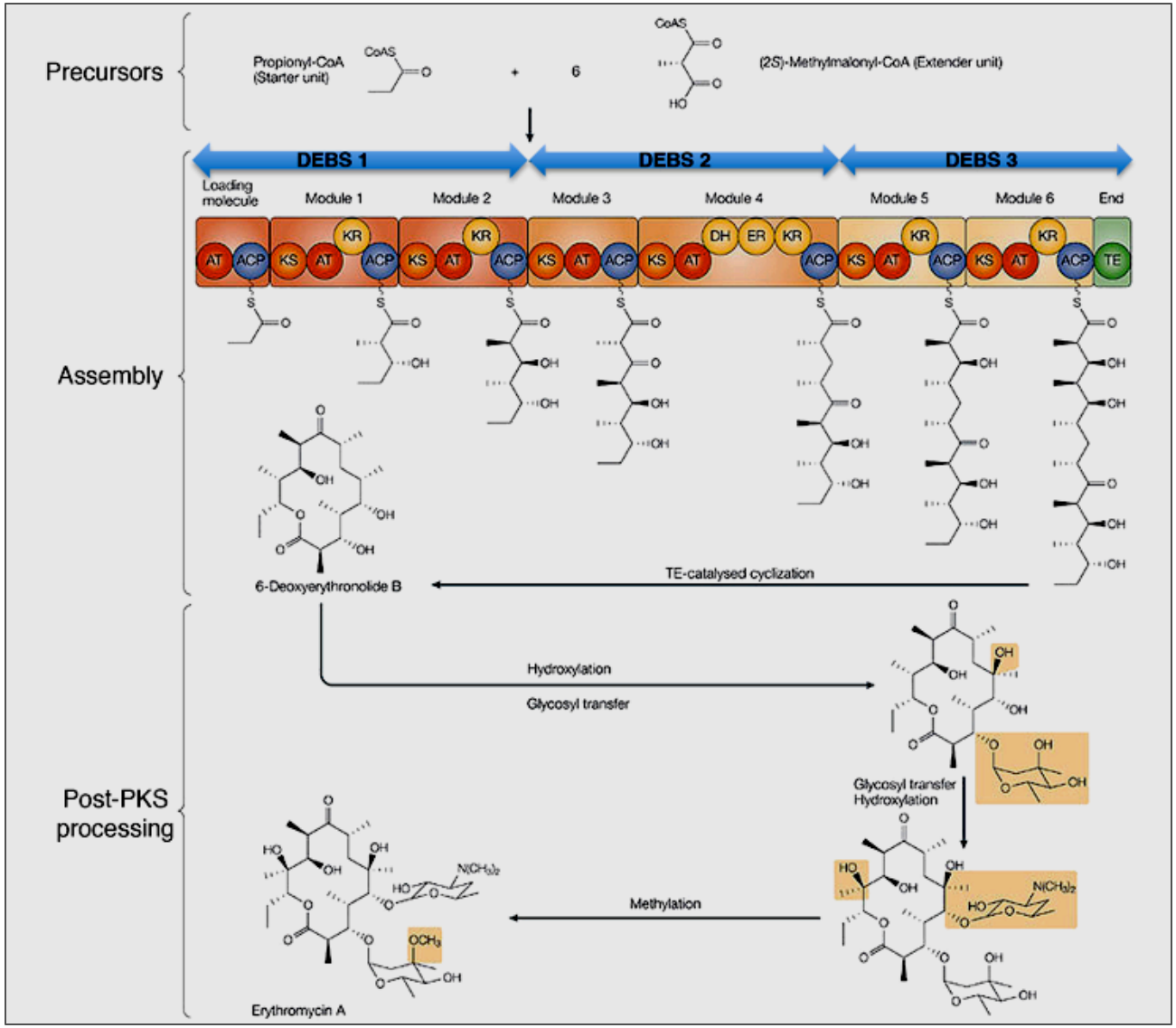
Natural Product Biosynthesis

- Biosynthesis of polyketides, NRPS well understood
- Modular in nature, analogous to FAS
- Organized in a linear array of domains, assembly line to form the ‘backbone’
- Domains are clustered in bacteria; include post-assembly processing enzymes and resistance genes



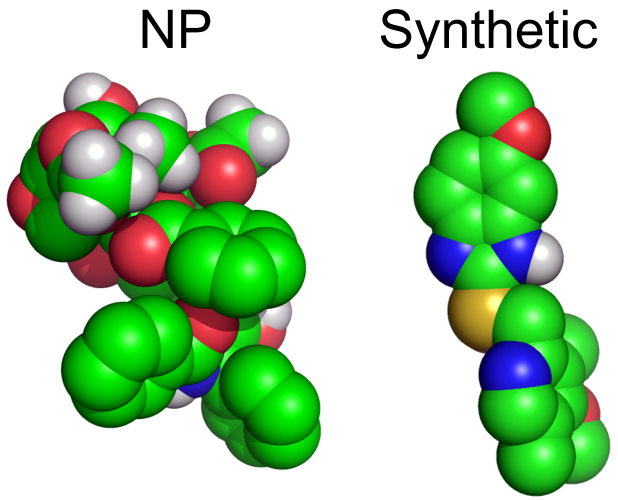
erythromycin

Example of polyketide biosynthesis: erythromycin A



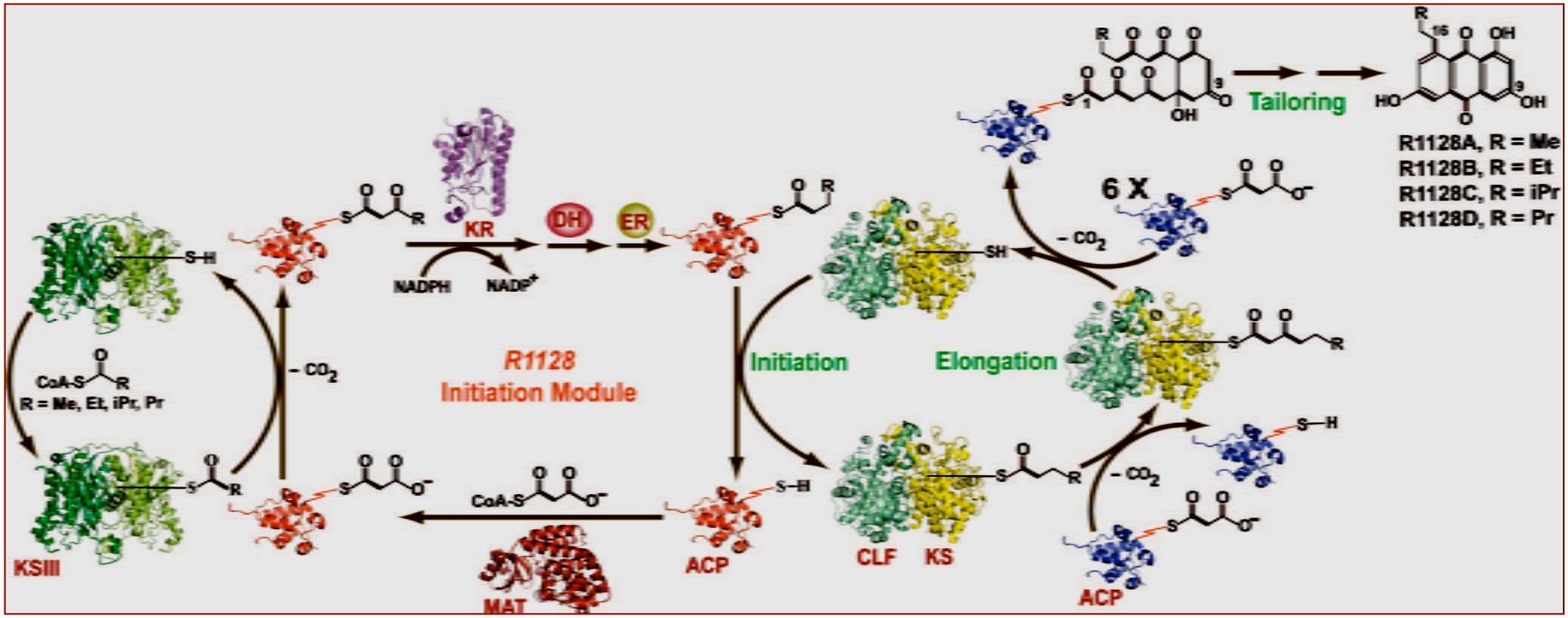
Weissman & Leadlay, *Nat. Rev. Microbiology*, 2005

What makes natural products unique?



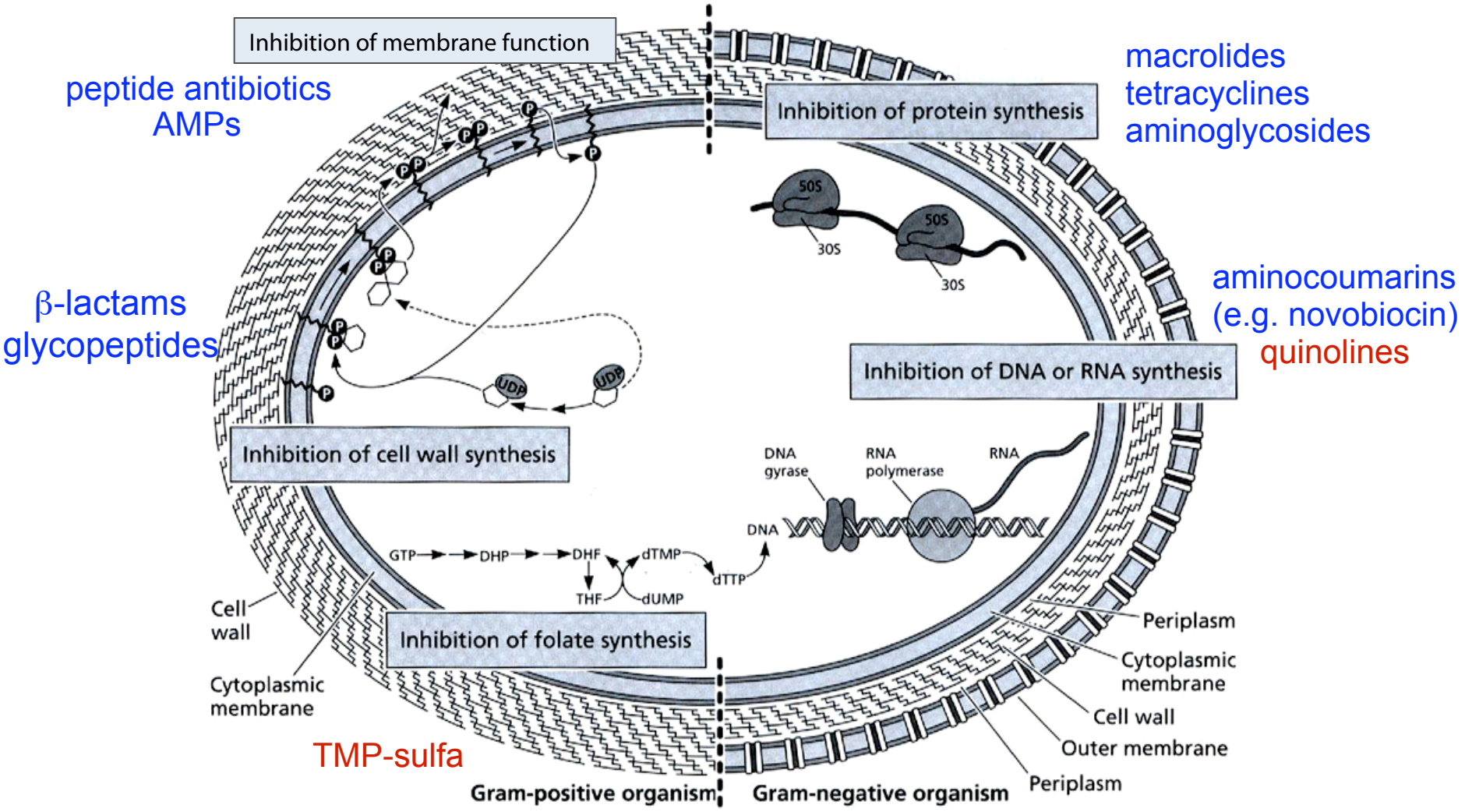
- Molecular complexity → biological activities
- Drug discovery: NPs occupy separate portions of chemical space
- Selected over 3.5 BA of evolutionary pressure
- Evolving in presence of biological receptors/organisms
- Mode of synthesis selects for protein recognition

Natural products are tailored to interact with biological systems



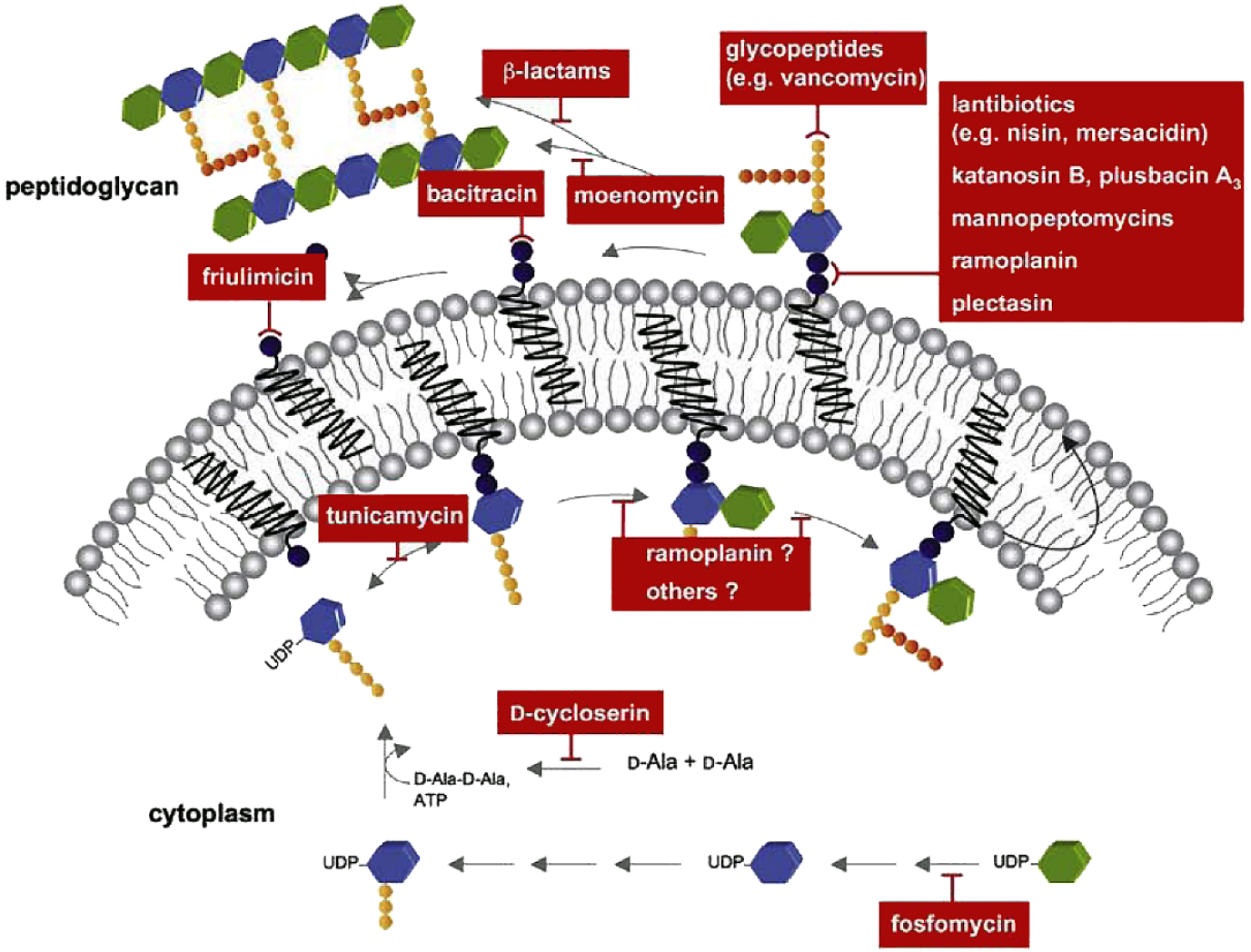
Biosynthesis of aromatic polyketides in bacteria, Das & Khosla, *Acct. of Chem. Res.*
And see video at http://www.scivee.tv/node/8551

Antibiotics, Targets



Mechanisms of Antibiotic Action and Resistance, C. Walsh, *Trends in Microbiology*, 2001

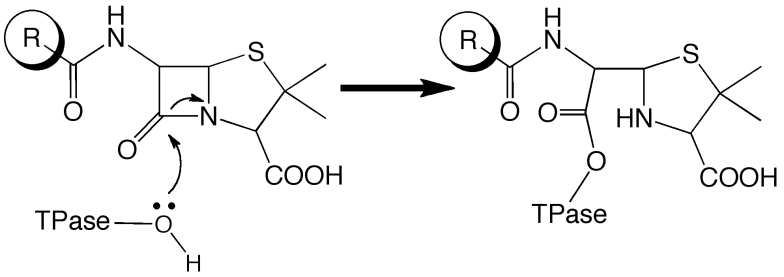
Natural Products as Antibiotics

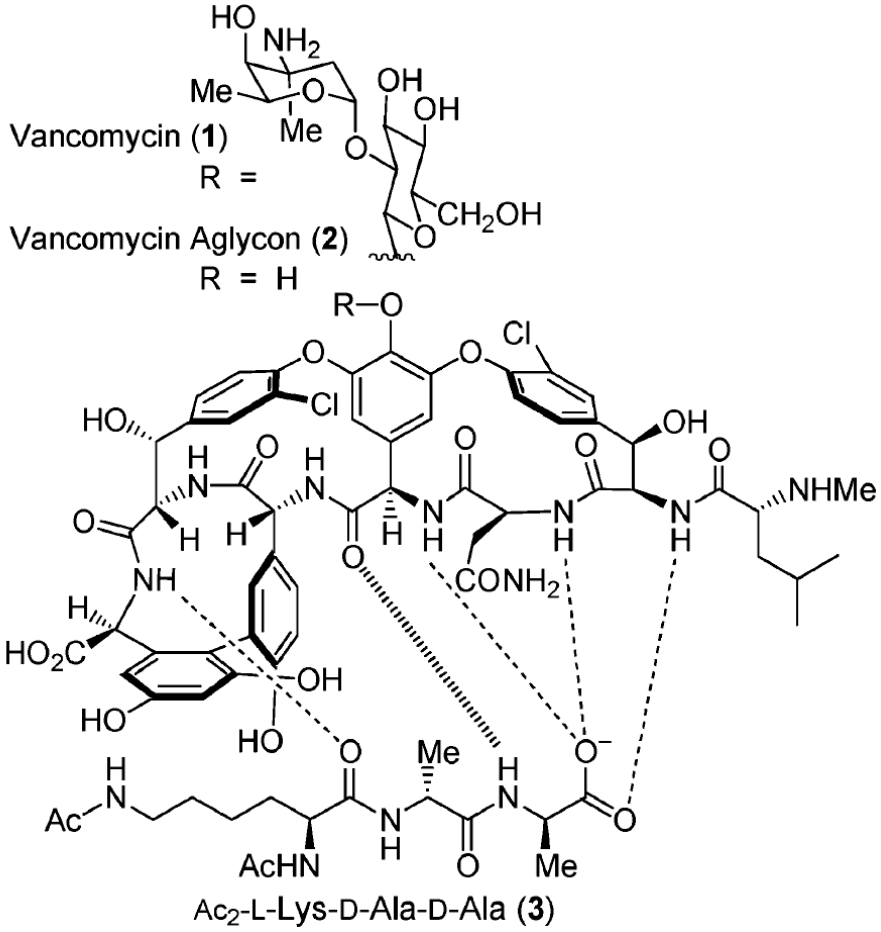


Schneider & Hall, *Int. J. Micrbiol*. 2010

Cell Wall Biosynthesis

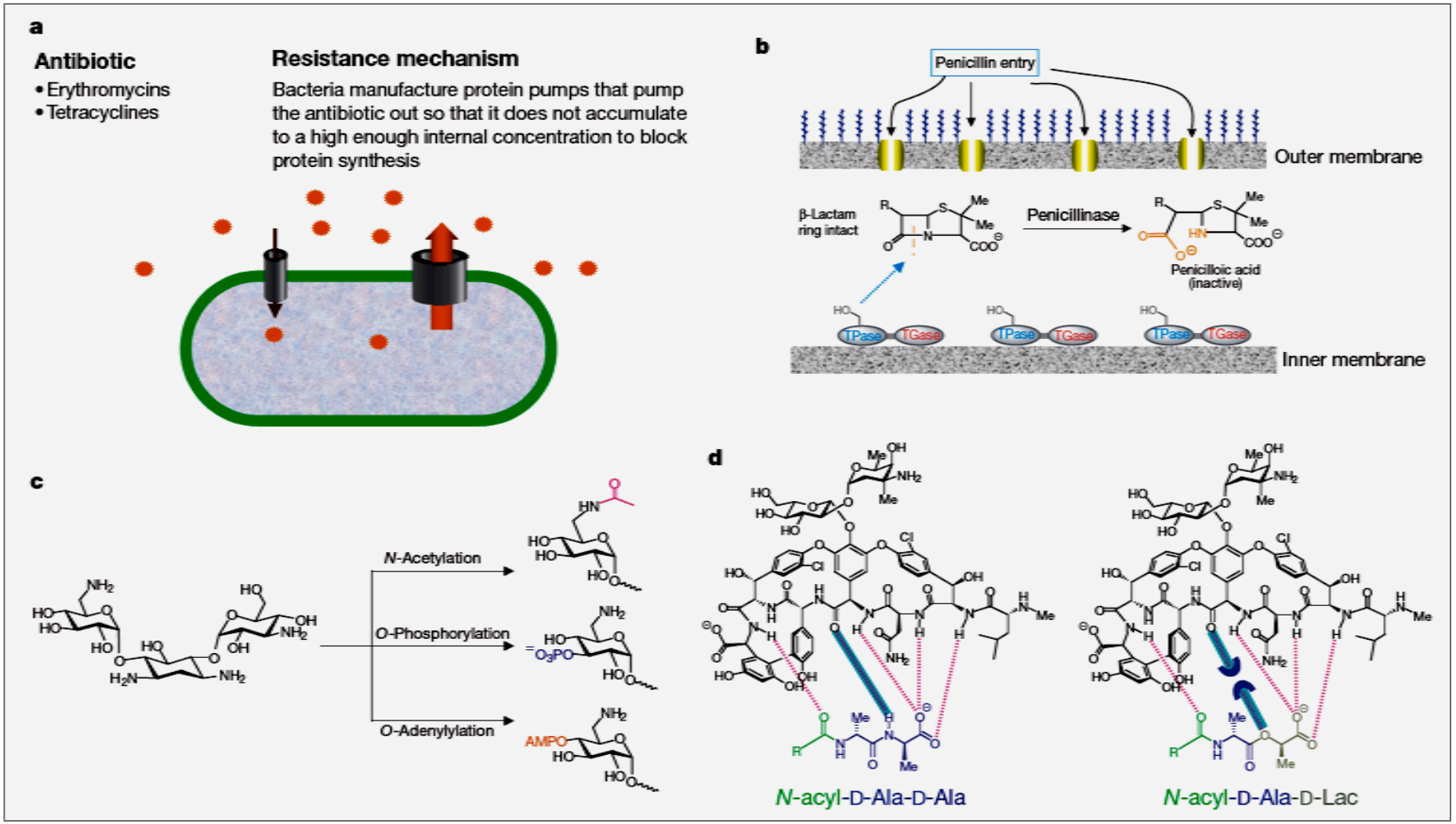
β-lactams inhibit transpeptidase





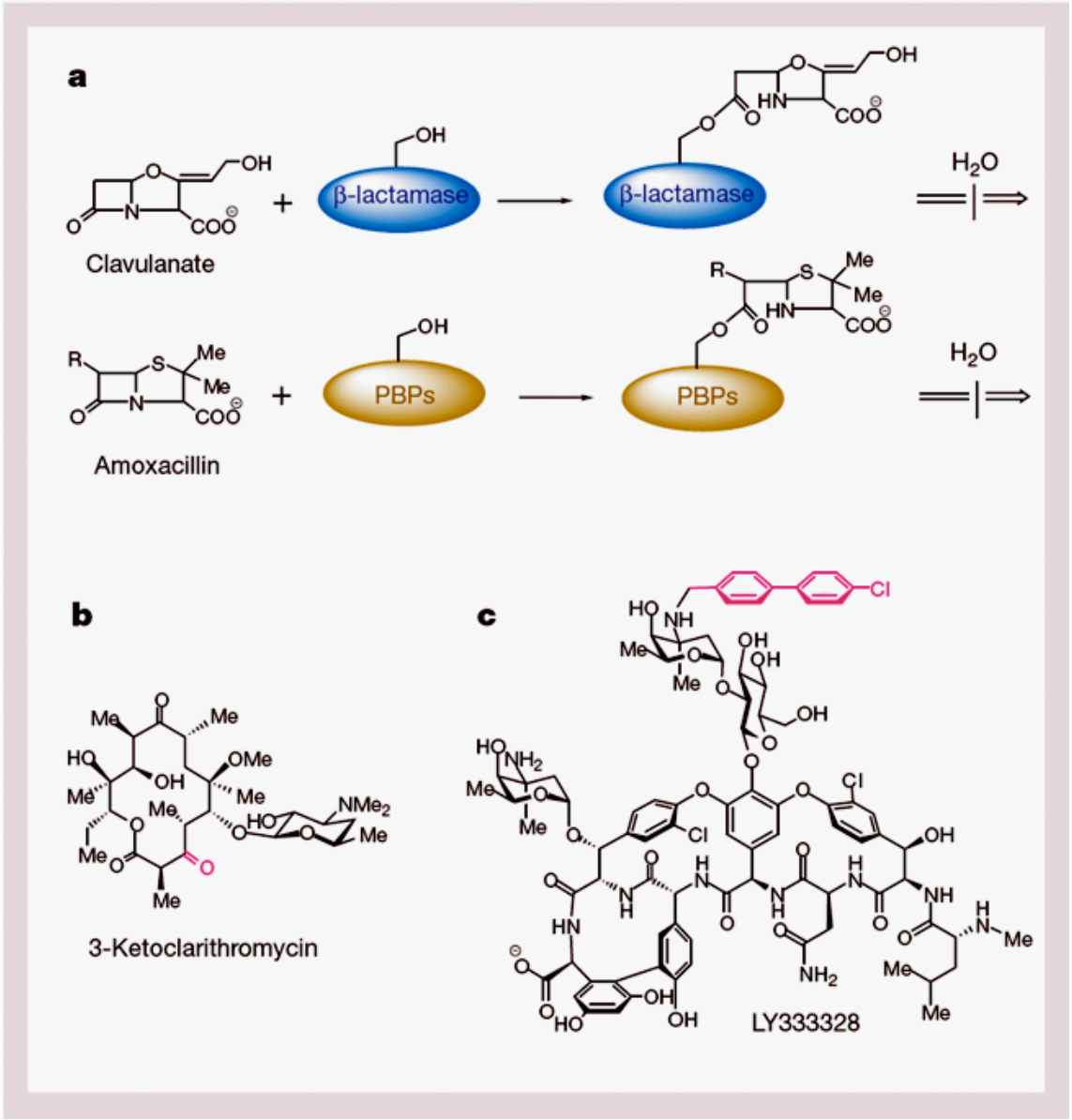
Glycopeptide antibiotics bind D-Ala-D-Ala
Prevent synthesis

Resistance Mechanisms



Walsh, C., *Nature Insight Reviews*, **2000**, *406*, 775-780

Strategies to Deal with Resistance



Walsh, C., *Nature Insight Reviews*, **2000**, *406*, 775-780

Future development of antibiotics

- Will require screening and development of all classes of molecules, synthetic and NPs
- Novel classes of molecules are needed
- New targets are needed; research active, but need more
- Bacterial genomics will contribute
- Need new sources!
- To manage resistance, use of antibiotics will need to change

For natural products-related questions, contact us:

Carole Bewley, NIDDK
caroleb@mail.nih.gov

David Newman, NCI
newmand@mail.nih.gov